

Andreas Bugge

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THIENO[2,3-b]THIOPHENE AND
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This review gives a summary and discussion of results from the following papers, which will be referred to by the capital letters A-K.

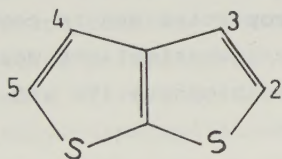
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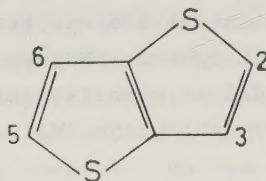
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INTRODUCTION

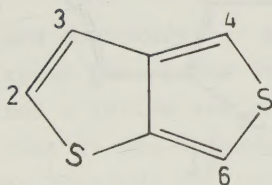
By the annelation of two thiophene rings, four isomeric thienothiophenes may be formed, namely the three classical isomers thieno[2,3-b]thiophene (I), thieno[3,2-b]thiophene (II), thieno[3,4-b]thiophene (III), and the fourth isomer, thieno[3,4-c]thiophene (IV), for which the only uncharged resonance contributors are structures containing tetravalent sulphur.



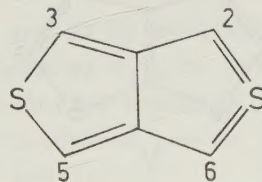
I



II



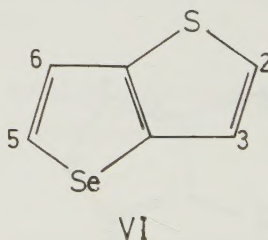
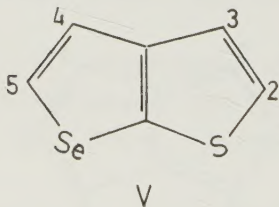
III



IV

Thieno[2,3-b]thiophene (I) was first described by Biedermann and Jacobson (1) in 1886, and thieno[3,2-b]thiophene (II) by Challenger and Harrison (2) in 1935. They are both stable compounds. I is a liquid at room temperature and II is a solid with m.p. 54° . The other two, III and IV, were first described as their unstable methyl derivatives (3,4). The unsubstituted compound IV is not yet known, but III was reported by Wynberg and Zwanenburg (5) in 1967 and described as a colourless oil, m.p. 7.5° , which turned yellow rapidly on standing in air.

While thiophene has been extensively studied for several decades, little work has been done on the thienothiophenes. Most of the earlier work on I and II was carried out by Challenger and his collaborators in the years 1935 to 1953 (2,6-12). In recent years, valuable contributions to the understanding of the chemistry of the thienothiophenes have been made by Goldfarb and his coworkers (13-25), mainly on the synthetic side. However, the development of new spectroscopic and analytical techniques prompted the author to take up the study of I and II in order to contribute to the understanding of their chemical and spectroscopic properties and to compare them with thiophene. NMR spectroscopic investigations were also extended to comprise seleno[2,3-b]thiophene (V) and seleno[3,2-b]thiophene (VI).



METHODS OF PREPARATION

Thieno[2,3-b]thiophene (I) was first prepared in very low yields by the treatment of citric or 1,2,3-propanetricarboxylic acid with phosphorous sulphide (1,26). Capelle (27) and others (28) passed acetylene into boiling sulphur and found limited amounts of a compound which was assumed to be I. This method was adopted by Challenger and Harrison (2) who managed to isolate I and II from the reaction mixture.

In 1953 Challenger and Holmes (11) found that pure II could be obtained in a yield of approximately 10 % by the cyclisation of (3-thienylthio)acetic acid with sulphuric acid to 2H,3H-thieno[3,2-b]thiophene-3-one, followed by reduction with lithium-aluminium hydride. This reaction was later studied by Gronowitz and Moses (29) who showed that the cyclisation product of (2-thienylthio)acetic acid also gave exclusively II after reduction. The cyclisation of both α -(2-thienylthio)-propionic acid and α -(3-thienylthio)propionic acid resulted in 2-methylthieno[3,2-b]thiophene (30) after reduction. A similar cyclisation reaction has been studied by Goldfarb et al. (15-18). On treating 2-(acetonylthio)-5-ethylthiophene with AlCl_3 they obtained a mixture of 2-ethyl-6-methylthieno[3,2-b]thiophene and 2-ethyl-4-methylthieno[2,3-b]thiophene, thus showing that migration of the acetonylthio group occurred. On the other hand, cyclisation of (3-acetonylthio)-5-methylthiophene resulted in 2-ethyl-6-methylthieno[3,2-b]thiophene only.

Tilak and coworkers prepared I and II by cyclising substituted thiophenes in the presence of P_2O_5 or polyphosphoric acid (for a review see ref. 31). Recently, Brandsma (73) has shown that 2- and 3-(propargylthio)thiophene can be transformed into the 2-methyl derivatives of I and II.

The best ways at present to obtain I and II are given by Gronowitz and Persson (32) and by Goldfarb et al. (18). Consequently, these methods were adopted by the author to prepare I and II (Paper A). The synthetic procedures are

largely the same. The starting material is thiophene, from which methyl(3-formyl-2-thienylthio)acetate and methyl(2-formyl-3-thienylthio)acetate are prepared, followed by a Claisen type condensation to the condensed ring systems.

The same synthetic approaches were employed by the author (Paper C) and by Goldfarb (33) in the preparation of seleno[2,3-b]thiophene (V) and seleno[3,2-b]thiophene (VI). However, it was found that the exchange of lithium with selenium was best performed in tetrahydrofuran solution instead of in ether.

Paper G and papers by Goldfarb and coworkers (13,14,17-19,24) describe similar cyclisation reactions for the preparation of alkyl-substituted derivatives of I and II.

Recent papers by Wright (34) and by Gronowitz and Maltesson (35) describe the ring-closure of some thiophene, selenophene and furanacrylic acids with thionyl chloride in the presence of pyridine. This reaction indicates a possible route to chlorine-substituted derivatives of I, II, V, and VI.

SUBSTITUTION REACTIONS

It is known, mainly through the work of Challenger (2,6-12), that like thiophene and benzo[b]thiophene, I and II have aromatic character, i.e., they undergo substitution reactions with electrophilic reagents. They can also be metalated with ethylmagnesium bromide. Direct metalation of I and II, carried out by Challenger (6,8), gave after carbonation the acids 2-carboxythieno[2,3-b]thiophene and 2-carboxythieno[3,2-b]thiophene in moderate yields. Dimetalation of II, and probably also of I, was observed, but the products after carbonation were not further investigated.

In Paper A a more detailed investigation of the metalation of I and II is described, with butyllithium as the preferred metalating agent. Treatment of I and II with one equivalent of

butyllithium in ether showed after carbonation that for both the isomers substitution in the 2- or α -positions had occurred. No indications of substitution in the β -positions or disubstitution were found in the IR and NMR spectra. Metalation of I and II with two equivalents of butyllithium in ether resulted in both cases in the formation of 2,5-dicarboxylic acids after carbonation.

From these results it is evident that in both I and II the 2-protons are the first subjected to substitution. Introduction of lithium in the 2-positions lowers the reactivities of the 5-positions to such a degree that dilithiation probably only occurs to a small extent, if at all, with less than one equivalent of butyllithium.

Halongenation. In papers by Challenger (2,7,12) I and II are reported to react readily with bromine, giving polybrominated derivatives. The isolation of monobromo derivatives is not reported. With one molecular proportion of bromine in glacial acetic acid, both gave polymers containing some bromine. In Paper D it is shown that if I and II are treated with equivalent amounts of N-bromosuccinimide (NBS) in glacial acetic acid, substitution in the α -positions occurs and the monobromo derivatives are obtained. The monobromo compounds with bromine in the 2-positions are unstable, decomposing in a few hours at room temperature, but can be kept for several days at -15° or in acetone solutions. With two molecular proportions of NBS the two 2,5-dibromo compounds can be prepared in the same way in good yields.

Quantitative determinations of the product mixtures by means of IR spectroscopy showed the presence of the unreacted thienothiophene, together with the 2-bromo- and the 2,5-dibromothiophenes. The results are summarized in Paper D and Paper J.

The possibility of an acid-catalysed rearrangement of the reaction products, similar to that reported by Gjøs and Gronowitz (36), was considered. However, no indication that

the bromination under the above conditions should be thermodynamically controlled was detected.

The 2,3,5-tribromo derivatives of I and II are accessible in good yields by bromination with three equivalents of bromine. Treatment of the two tribromo derivatives with excess zinc in glacial acetic acid gave the 3-bromo derivatives of I and II. Treatment of 2,3,5-tribromothieno[2,3-b]thiophene with a smaller amount of zinc under the same conditions gave the 2,4-dibromo derivative of II.

Attempts to prepare 2,4-dibromothieno[2,3-b]thiophene from 2,3,5-tribromothieno[2,3-b]thiophene by halogen-metal interconversion at -70° were not successful. Instead of the expected dibromo compound, a ring-opening reaction had obviously taken place. The reaction product is believed to be 2-(5-bromo-3-ethynyl-2-thienylthio)-3,5-dibromothieno[2,3-b]thiophene, but other structures are not excluded. The arguments leading to the above conclusion are given in Paper D.

A similar ring-opening reaction of 3-bromobenzo[b]furan was observed by Reichstein and Baud (37) and later studied by Melstrom (38) and by Gilman and Melstrom (39). Recently, analogous ring-opening reactions were discovered in benzo[b]-thiophene (40), selenophene (41-42), and thiophene (43).

The chlorination of I and II is reported in Paper J. Mono- and dichloro derivatives of I and II may be synthesised by chlorination of the thienothiophenes with N-chlorosuccinimide (NCS) in glacial acetic acid. With two molecular proportions of NCS good yields of the 2,5-dichloro derivatives of I and II are obtained. Treatment of I and II with equimolar quantities of NCS resulted in mixtures in which the major products are the 2-chloro derivatives together with the starting materials and the 2,5-dichlorinated products. These mixtures were similar to those obtained in the brominations with NBS. The compositions of the reaction mixtures are given in Paper J. In the way described above, thiophene was chlorinated with one equivalent of NCS, and gave a similar mixture of products (Paper J).

From the discussion in Paper J it may be concluded that a halogen in the 2-position in I obviously deactivates the 5-position to a greater extent than is the case with II and thiophene. The 3-chloro derivatives of I, II, and thiophene were prepared via the 3-bromo derivatives by halogen-lithium interconversion at -70° followed by treatment with molecular chlorine in hexane.

The tendency of the 2-bromo derivatives to decompose made it pointless to try to determine the extent of β -substitutions in the bromination reactions. In the chlorination reactions, on the other hand, the $\alpha:\beta$ isomer distributions were determined.

Formylation. The Vilsmeier formylation of I and II is discussed in Papers G and J. For both the isomers the major reaction products were the α -substituted products.

The 3-formyl derivatives of I and II were prepared from the 3-bromo derivatives by halogen-metal interconversion at -70° followed by treatment with N,N-dimethylformamide (DMFA).

Analyses of the reaction mixtures showed that to a small extent formylation in the 3-position in I had occurred. In II the 3-formylated isomer was not detected; i.e. if present the amount is considered to be less than 0.1 %. Formylation of thiophene under the above conditions resulted similarly in undetectable amounts of the β -isomer. The isomer distributions and $\alpha:\beta$ reactivity ratios are given in Paper J.

From the formyl derivatives the corresponding methyl derivatives (Paper G) and cyano derivatives (Paper K) were prepared, following conventional procedures.

Acetylation. The tin(IV)chloride catalysed acetylation of I and II (Paper J) was carried out in 1,2-dichloroethane solution with acetic anhydride or in carbon disulphide solution with acetylchloride. Both methods resulted in the 2-acetyl derivatives as the major products. Acetylations in the 3-positions in I and II by reaction with acetic anhydride were

evident from gas chromatography and mass spectra. Investigations by Marino et al. (44) show that in the acetylation of thiophene under the same conditions, acetylation of the β -position in thiophene occurs to approximately the same extent.

Nitration. Nitration of I and II with copper(II)nitrate trihydrate in acetic anhydride gave the 2-nitro substituted derivatives as the major reaction products (Paper J). The yields are about the same as those obtained by Challenger (2) by treatment of I and II with acetyl nitrate at -10° .

The amounts of 3-nitrothieno[2,3-b]thiophene obtained differed considerably from one reaction to another. In the light of a recent paper by Hogget, Moodie and Schofield (45) this is perhaps not so surprising, since they have found that nitration via nitrosation, particularly for very reactive substrates, probably accompanies another process of nitration. They base their results on nitrations with acetyl nitrate in acetic anhydride. The use of copper(II)nitrate trihydrate in acetic anhydride has not been investigated to a great extent, but results by Gronowitz and Gjøs (46) on the nitration of 2-phenylthiophene make it reasonable to believe that the same reagents are operative in the acetyl nitrate and in the copper(II)nitrate method.

The nitration of thiophene has been investigated by Østmann (47), who found a much higher percentage of 3-nitrothiophene (15 %) than is the case for I and II.

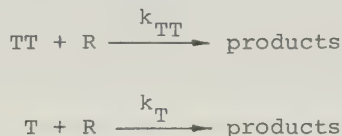
REACTIVITY

As mentioned in the previous section, it is evident that the α -positions in I and II are far more reactive than the β -positions, both in electrophilic aromatic substitutions and in metalation with butyllithium. In this they both resemble thiophene.

The reactivities of thiophene and of benzo[b]thiophene towards electrophilic reagents have been extensively investigated by Marino and coworkers (44) and the reactivities of the α - and β -positions were determined relative to benzene. Comparatively little is known about the thienothiophenes. Only a paper by Goldfarb and Shatenstein (48) on the rate of electrophilic deuterium hydrogen exchange in I and II relative to thiophene is known to the author.

An investigation of the reactivity of I and II can be made by first determining the overall reactivities relative to thiophene for a number of reactions.

The overall relative reactivities are conveniently determined in competitive experiments, in which mixtures of I or II and thiophene are reacted with insufficient amounts of a common reagent or reactive intermediate. The reactions can be expressed in the equations



where TT is I or II, T is thiophene and R is the common reagent. k_{TT} and k_{T} are the reaction rates for the reaction between I or II and R, and between thiophene and R, respectively.

Provided that the order of the reaction can be ascertained from an inspection of the above equation and that the analyses of the reaction products will reflect the forward reaction only, the relative rates can be calculated from the equation

$$\frac{\log(\text{TT})_i / \log(\text{TT})_j}{\log(\text{T})_i / \log(\text{T})_j} = \frac{k_{\text{TT}}}{k_{\text{T}}} \quad (\text{I})$$

where $()_i$ and $()_j$ denote the initial and final concentrations.

With knowledge of the $\alpha:\beta$ isomer distributions for the thienothiophenes and thiophene, the partial rates relative to the β -position in thiophene can be calculated from the equation

$$\frac{r_{TT \alpha \text{ or } \beta}}{r_{T \beta}} = \frac{k_{TT} \frac{1}{2}(\text{fraction of } \alpha \text{ or } \beta \text{ substituted TT})}{k_T \frac{1}{2}(\text{fraction of } \beta \text{ substituted T})} \quad (\text{II})$$

where r_{TT} is the partial relative rate of the α or β position in I or II.

Overall reactivities relative to thiophene were determined for the metalation of I and II with butyllithium in ether (Paper A), the acetylation with acetic anhydride catalysed by tin(IV) chloride in 1,2-dichloroethane, the Vilsmeier formylation in 1,2-dichloroethane, and the chlorination with NCS in glacial acetic acid at 25⁰ (Paper J). The overall relative reactivities were calculated using equation I, and the results are summarised in Paper J. The competitive experiments were carried out at three different concentrations. This was done to establish whether or not any concentration effects were operative. However, the calculated overall relative reactivities were within the experimental error.

In the metalation experiments the reaction mixtures were hydrolysed after one minute with a mixture of CH₃COOD and D₂O. The resulting mixtures of I or II and thiophene and their 2-deuterio derivatives were analysed on a mass spectrometer interfaced with a gas chromatograph. The ratios in mole percent between the unsubstituted and deuterated components were determined according to Biemann (49).

Transmetalation in the thiophene series has previously been described by Moses and Gronowitz (50). Because of this, transmetalation experiments between 2-lithiothiophene and I or II and between the two 2-lithiothienothiophenes and thiophene were performed. These experiments showed that a state of equilibrium existed between the metalated and unmetalated components, but that the rate of transmetalation is so slow

that the error introduced in the competitive experiments will be small compared with the error in the analysis of the reaction mixtures. Because of the slowness of the transmetalation reactions, side reactions, possibly due to cleavage of the ether (51), made it impossible to determine the state of equilibrium.

In the competitive acetylations, acetic anhydride was preferred rather than acetyl chloride since a weaker acid was liberated in the course of the reaction. As solvent 1,2-dichloroethane was selected since, according to Jensen, Marino and Brown (52), it is particularly suitable for Friedel-Crafts acylations. In contrast with the acylation of benzene derivatives, the catalyst required was only 0.01 mole for each mole of acetic anhydride. Marino (44) suggests that "this is probably due either to the greater reactivity of the substrates or to the lower ability of the ketones formed to coordinate the catalyst".

The overall reactivity of thiophene relative to benzene on acetylation has previously been determined by Linda and Marino (53) under the above conditions to be $9 \cdot 10^5$. Using this value, the overall reactivities of I and II relative to benzene are calculated to be $2.8 \cdot 10^6$. The overall relative reactivities found in the acetylations of I and II appear to be equal within the experimental error. In order to establish whether a difference in reactivity existed, a mixture of equimolar quantities of I and II was acetylated. The amounts of acetylated products were, however, the same within the experimental error, i.e. the overall relative reactivity is the same for I and II on acetylation.

The kinetics of the Vilsmeier formylation of thiophene derivatives in 1,2-dichloroethane has been studied by Marino et al. (54). Their results substantiate the current hypothesis on the mechanism of the reaction. Since there is no reason to believe that the mechanism is not the same for the formylation of I and II in 1,2-dichloroethane, this solvent was used in the competitive formylation experiments.

With electrophilic reagents such as the tin(IV)chloride-acetic anhydride adduct, the selectivity is poor; the reactivity of the thienothiophenes is about equal, and only about three times that of thiophene. In the Vilsmeier formylations and the chlorinations the difference in reactivity between I and II is clear; the latter is more reactive. This reactivity order is contradictory to the results obtained by Goldfarb and Shatenstein (48) in their electrophilic deuterium hydrogen exchange experiments. Actually, the difference is so small that only very "selective" reagents seem to be able to discriminate between the compounds.

In a recent paper, Clark (55) calculated the reactivity of thiophene and the isomeric thienothiophenes using the semiempirical PPP SCF MO method. He found, in agreement with the present investigations, that in electrophilic aromatic substitutions the 2-position in both I, II and thiophene is clearly favoured. Further, using table 5 in his paper, the calculated reactivity order for the site of highest reactivity in each compound is $I > II > \text{thiophene}$.

Partial relative reactivities. In the cases where the overall reactivities for I and II relative to thiophene and also the $\alpha:\beta$ isomer distributions were known, the reactivities of the α - and β -positions in I and II relative to the β -position in thiophene were calculated using equation II. The results are given and discussed in Paper J. The reactions studied are too few for any conclusive comparisons to be made between the compounds I, II, and thiophene. All the same, a reactivity order for the different positions in I, II, and thiophene is indicated in the paper, namely:

$\alpha \text{ in II} \approx \alpha \text{ in I} > \alpha \text{ in thiophene} > \beta \text{ in I} \approx \beta \text{ in II} > \beta \text{ in thiophene}$.

In the same paper comparison with benzo[b]thiophene is made.

In order to discriminate between the chemically similar substituted thienothiophenes and to determine the substitution pattern in I and II, NMR spectroscopy has proved to be an invaluable tool. A thorough study of the NMR spectroscopic properties of these compounds and the selenothiophenes was therefore found worthwhile. The results are reported in the Papers E, F, and H.

In previous papers, Gestblom et al. (56) analysed the PMR spectrum of II. The coupling constants were found to be $J_{23} = J_{56} = 5.25$ Hz and $J_{26} = J_{35} = -0.20$ Hz. Two additional cross-ring couplings $J_{AA'} = 1.55$ Hz and $J_{BB'} = 0.75$ Hz were detected but could not be assigned to definite couplings in the molecule. The spectra of the 2- and 3-bromo substituted II provided the necessary evidence for the assignments; i.e. the largest cross-ring coupling $J_{AA'} = J_{25} = 1.55$ Hz and the smallest $J_{BB'} = J_{36} = 0.75$ Hz are transmitted over six and five bonds respectively (Paper E). These results are in agreement with the arguments in Paper A and by Litvinov and Frankel (24).

The PMR spectrum of I exhibited an $AA'BB'$ spectrum similar to that of II, and was analysed using an exact $AA'BB'$ treatment. The derived coupling constants are given in Paper E. From the analysis one can not assign the couplings $J_{AA'}$ and $J_{BB'}$ to definite couplings in the molecule. However, the spectra of the 2- and 3-bromo derivatives of I supplied the necessary evidence for a complete elucidation of the coupling pattern in I.

The study of NMR parameters in group VI heterocycles was extended to comprise seleno[2,3-b]thiophene (V) and seleno-[3,2-b]thiophene (VI) (Paper F). The NMR spectra of V and VI both exhibited ABCD patterns. The proton resonances in the selenophene parts of the spectra were found to occur at lower fields than the corresponding protons in the thiophene part. This is in accord with previous investigations on selenophenes

and thiophenes, where a stronger shielding in thiophenes is attributed to a more effective lone-pair conjugation of S than of Se (57). The vicinal couplings between the protons in the selenophene parts of V and VI are larger than the corresponding couplings in the thiophene part, in agreement with observations (57,58) that selenophene couplings are larger than the corresponding thiophene couplings.

In addition to the proton-proton spin couplings, interactions between the ^{77}Se isotope of spin 1/2 and the protons in the selenophene parts of V and VI were discovered. Similar couplings in selenophenes have recently been studied by Gronowitz, Johnson and Hörnfeldt (72).

The cross-ring proton-proton couplings in V and VI do not only show the same general patterns as those in I and II, but the two sets of coupling constants are equal to within a few hundredths of a Hz, even in the couplings transmitted via six bonds. This would indicate a close similarity in the electronic structure and the geometrical shape of the selenothiophenes and the corresponding thienothiophenes.

Compared with other aromatic and heteroaromatic systems, the J_{36} couplings in II and VI can be classified in the same category as the majority of the reported cross-ring couplings in aromatic systems; i.e. couplings between protons separated by five bonds placed in a zig-zag structure. In the same category belong the much larger J_{25} couplings in both the thienothiophenes and selenothiophenes. They are all transmitted via the heteroatoms and follow a straight zig-zag path over six bonds. A similar large cross-ring coupling over six bonds was found in N-benzylthieno[3,2-b]pyrrole (59). In benzo[*b*]thiophene (60) the J_{26} coupling over six bonds is smaller than the J_{37} interaction over five bonds, but is still large compared with the presumably small or zero J_{25} coupling over six bonds not transmitted over the sulphur atom. The heteroatoms therefore seem to play an important role in the transmission of these long-range couplings. The cross-ring couplings over 4 and 5 bonds in I, II, V, and VI not following

a straight zig-zag path were, on the other hand, found to be small or zero. This seems to confirm the importance of a straight zig-zag path for long-range cross-ring interactions in poly-ring aromatic systems.

In marked contrast to the results given for I and V are the parameters assigned by Olsen and Snyder (61) to the structurally similar molecule N-benzylthieno[2,3-b]pyrrole. This is discussed in Paper E.

Aldehyde couplings are believed to be transmitted within the σ -electron framework, and in aromatic aldehydes, they show the same stereospecific behavior of being large only along straight zig-zag paths (62,63). Methyl couplings, on the other hand, are known to be transmitted through the π -electron framework. Hoffmann and Gronowitz (64,65) have predicted that on replacement of a ring proton with a methyl group the π -electron-transmitted coupling should remain almost unchanged in magnitude, but with reversed sign. According to this prediction, some insight into the nature of long-range couplings in I and II should be obtained by studying the PMR spectra of some methyl and formyl substituted derivatives (Paper H).

The spectra of the 2-formyl derivatives of I and II both showed long-range couplings between the formyl protons and the 5-protons and ortho couplings to the 3-protons. Couplings between the ring-protons and the aldehyde protons in the 3-formyl derivatives of I and II were not detected except for a small coupling, J_{4-CHO} , in I. From the discussion in Paper H it is evident that the large cross-ring couplings J_{25} in I and II are substantially reduced in the 2-formyl derivatives. Such a reduction of the coupling can be expected with the increasing number of bonds if a σ -electron interaction is assumed for the contact coupling. The ortho couplings in the aldehyde-substituted thienothiophenes seem to exist only when the formyl group is in the 2-position. This coupling has not previously been reported in thiophene, but is known in fluorothiophenes (66).

Long-range couplings between the methyl group and the protons in the other ring were only detected in the 2-methyl and the 2,6-dimethyl substituted derivatives of II. Relative to the unsubstituted compounds, the couplings do appear to be of finite magnitude and with reversed sign. According to Hoffmann and Gronowitz (64,65), this would indicate that the coupling $J_{2\text{CH}_3-5}$ in II should be partially π -electron transmitted. The $J_{3\text{CH}_3-6}$ coupling in II is zero while the J_{36} coupling in II is 0.75 Hz. For the same reasons as mentioned above this coupling should not be π -electron transmitted.

The results from this investigation do not give conclusive evidence concerning the nature of the cross-ring contact couplings. However, it seems evident that some other mechanism than a π -electron transmitted coupling is likely with the possible exception of the J_{25} coupling in II. These results are in agreement with the suggestion of Banwell and Sheppard (67) of a residual σ -induced long-range coupling which persists for straight zig-zag paths.

α -substituent effects on the proton chemical shifts. The influence of substituents on the NMR parameters has been extensively studied (see ref. 68 for a review) and attempts have been made to correlate chemical shifts and coupling constants with the electronegativity of the substituents or with different sets of substituent parameters. One way in which this has been done is to correlate the NMR parameters with the Hammett substituent constants σ_m and σ_p or one of their many modifications. Recently a new set of substituent constants was derived by Swain and Lupton (69); namely the field or inductive constants F and the resonance constants R . They are calculated from Hammett σ_m and σ_p values by assuming that any set of substituent constants (σ_m , σ_p , σ^- ...) may be expressed as a linear combination of the type $fF + rR$. The constants F and R are different for each substituent and independent of reaction, solvent and temperature. The letters f and r denote empirical weighting factors and are independent of the substituents, but different for each ring system and site of substitution. The

substituent constants F and R are mainly obtained from reactivity measurements on benzene derivatives. Recently Rodmar, Gronowitz and Rosén (70) have shown that chemical shifts and spin-spin coupling constants of thiophenes, fluorothiophenes, and selenophenes (71,72) can be correlated with the substituent parameters of Swain and Lupton.

In Paper K the proton chemical shifts of a number of 2-substituted derivatives of I and II have been correlated with the substituent constants F and R by means of the linear two parameter equation

$$\delta_H = i + fF + rR$$

where δ_H is the proton chemical shift and i is the intercept. Comparisons with 2-substituted thiophenes were also made. From the computed correlation coefficients, 0.97 or better, it is evident that a correlation exists between the proton chemical shifts of the thienothiophenes and the substituent constants of Swain and Lupton (69). The results, discussed in Paper K, indicate that the field effect F contributes significantly to the proton chemical shifts of all the ring protons in I and II. The resonance contributions are, on the other hand, in some cases important for substituents with large R values only. Comparison with similar calculations on thiophene show that in the fused ring systems I and II the inductive effect plays a more important role than is the case in thiophene. In thiophene the field effect is important for the 3-proton shifts, while for the other protons it is important for substituents with large F values only.

The regression constants f and r are influenced by the choice of substituents. This is evident from a comparison of the regression equations of thiophene, when calculated with two different sets of substituents. It is therefore clear that too far reaching conclusions concerning the relative importance of the field and resonance effects on the proton chemical shifts should not be drawn when relatively few substituents are used to compute the regression equations.

The effect of a lithium substituent on the PMR parameters.

A most interesting effect on the PMR parameters was found in the 2-lithium derivatives of I and II (Paper A). In both compounds a downfield chemical shift of the 3-protons was observed, relative to the unsubstituted compounds. On the other hand, the protons in the annelated rings shifted towards higher field.

In order to see whether a similar effect was operative in the thiophene series, a number of lithiated thiophenes was studied (Paper B), and this was indeed the case. The spectrum of 2-thienyllithium showed that not only the 3-proton, but also the 4- and 5-protons shifted towards lower field. Similar comparisons of the chemical shifts of some lithiated bromothiophenes showed downfield shifts of all of the protons. Downfield proton shifts were found in 3-thienyllithium too, but the extent of the effect is not clear due to the strongly coupled spectrum of this compound. 3-Bromo-4-thienyllithium showed chemical shifts similar to those of 3-bromothiophene.

From PMR studies of alkylolithium compounds (74), it has been found that protons on the carbon atoms α to the metal shift upfield relative to those on the β carbons. This is explained in terms of the strongly electron-donating property of the lithium atom. It is therefore rather unexpected to find that in vinylolithium (75) the protons on the α carbon shift towards lower field than those on the β carbons. This same anomaly is observed in several aromatic organometallic compounds of lithium, magnesium, and calcium, and indicates that other factors than local charge densities strongly contribute to the chemical shifts. In these compounds the protons "ortho" to the metal are the only ones deshielded with respect to benzene. This is contrary to what is found for thiophene.

In recent papers by Ladd (76-78) and by Fraenkel (79,80) this anomaly has been discussed. Ladd (76,78) assumes that the phenomenon can be explained by the magnetic anisotropy of the carbon atom involved in the carbon-lithium bond. This explanation may seem plausible in view of the results obtained on phenyllithium and the two lithiated derivatives of I and II.

In the case of 2-thienyllithium, all the protons show marked downfield chemical shifts. If Ladd is correct this would imply that the above-mentioned magnetic anisotropy effect should produce a deshielding not only of the "ortho" protons, but of all the ring protons.

Fraenkel (79,80), on the other hand, proposes that since the phenyl anion and pyridine are isoelectronic, the two species should have similar electronic structures. Consequently, to the degree that the carbon-metal bond is ionic, the same effects should account for the shifts in pyridine and in phenyllithium. These considerations are based on similarities in the PMR and UV spectra of some pyridines and some aromatic organometallic compounds. In the thiophene series one should similarly expect the same effects to be operative in the isoelectronic species isothiazole and the 2-thienyl anion and thiazole and the 3-thienyl anion.

Substituent	Chemical shifts ^a				J ₂₅	J ₃₄	J ₃₅	J ₄₅
	H-2	H-3	H-4	H-5				
Isothiazole	-	1.46	2.74	1.22	-	1.6	<0.4 ^b	4.6
2-Thienyl-lithium	-	2.48	2.82	2.34	-	2.8	0.5	4.3
Thiazole	1.14	-	2.09	2.56	2.0	-	0-0.5 ^c	3.2
3-Thienyl-lithium	Strongly coupled spectrum. Largest peaks at 2.31 and 2.94.							
Thiophene	2.67	2.92	2.92	2.67	2.75 ^d	3.45 ^d	1.05 ^d	5.15 ^d

a. τ -values relative to TMS in ether solution.

b. ref. 81 c. ref. 82 d. ref. 83

An inspection of the above table reveals no striking resemblance between thiazole and 3-thienyllithium or between isothiazole and 2-thienyllithium. In the case of the latter some likenesses may all the same be found; the protons all shift towards lower

field and the coupling constants are significantly reduced relative to thiophene. The absence of UV spectra of the compounds in question makes a further discussion of the spectroscopic properties fruitless.

It is known that phenyllithium exists in ethereal solution as a dimer. This has been discussed by Ladd (76,78) and in Paper B. Ladd assumes an Li-C-Li angle of the dimer of approximately 70° . With this angle of the dimer he is of the opinion that his conclusions are not inconsistent with a dimeric structure in solution. The author, on the other hand, finds that as long as the geometry of the dimer in solution is not known, too far-reaching conclusions may not be drawn.

Compared with the well-established intervals for the four proton-proton coupling constants in thiophenes, a lithium substituent causes a marked decrease in the magnitude of the couplings. This, too, was observed by Ladd (76,78) and by Fraenkel (79,80) in their investigations, where all but the J_{25} couplings are smaller than the typical values for covalently substituted benzenes. The existence of a relationship between proton-proton coupling constants and substituent electronegativity has been demonstrated for example in monosubstituted benzenes (84). A similar correlation between the magnitude of thiophenic coupling constants and the electronegativity of the substituent has recently been demonstrated by Bulman (85) in 2-substituted thiophenes. He found that the three proton-proton coupling constants in these compounds vary linearly with the electronegativity of the substituent, ranging in electronegativity from lithium to fluorine.

Mass spectroscopy. In search of a convenient and specific method for the determination of I and II and their derivatives, mass spectroscopy was considered. A study of the mass spectroscopic properties of I and II is given in Paper I.

An examination of the mass spectra soon revealed that the compounds I and II exhibited the same fragmentation pattern. With the help of metastable defocusing it was further shown

that in the excited state both compounds probably isomerise into a common structure or at least that II will undergo skeletal rearrangement into I. This assumption is the conclusion of a discussion of the fragments m/e 64 and m/e 76. The fragment m/e 64, $C_5H_4^{\cdot+}$, is present in the spectra of both the compounds and is found to originate from the molecular ion by the loss of CS_2 . The fragment m/e 76 was shown by high resolution to be a doublet containing $CS_2^{\cdot+}$ and $C_6H_4^{\cdot+}$ in the approximate ratio of 5:1. By measurement of the ionisation potentials of authentic CS_2 and of CS_2 from the compounds it was clear, however, that a contribution to the formation of $CS_2^{\cdot+}$ through pyrolysis could not be excluded.

In an unpublished extension of the above work the α and β monoformyl and the α and β monomethyl derivatives of I and II and the compounds 2,4-dimethylthieno[2,3-b]thiophene and 2,6-dimethylthieno[3,2-b]thiophene were studied. The fragmentation pattern of the compounds indicated that a skeletal rearrangement similar to that mentioned above possibly also took place in the substituted compounds. The spectra of the four monomethyl substituted thienothiophenes exhibited the same fragmentation pattern. The same was found from comparisons of the spectra of the other isomeric compounds mentioned above. Consequently it is evident that mass spectroscopy is not a useful tool for the specific identification of different isomeric thienothiophenes.

Since the molecular ions are strong peaks, in fact they are the base peaks, in the spectra of I and II, this property was used in Paper A to analyse the extent of deuteration in I and II after lithiation and lithium deuterium exchange.

Other spectroscopic investigations. Apart from papers by Zhizhin and Goldfarb (25) and Zhizhin et al. (90) on some IR and Raman spectroscopic investigations of II no work is known to the author on vibrational spectroscopic studies of I and II.

The UV spectra of I, II, and III have, on the other hand, received some attention. The electronic spectra of I and II have been investigated in solution and in the vapor phase by

Padhye and Patel (86). The spectra in solution of III and of some substituted derivatives of I and II have been published by Wynberg and Zwanenburg (5) and by Goldfarb and Litvinov (17,18). Theoretical calculations of electronic transitions and other observables in I, II, III, and other sulphur heterocycles have been made by Clark (87), Johnstone and Ward (88) and by Skancke and Skancke (89), and the predicted values assigned to observed transitions in the spectra.

Recently a study of the photoelectron spectra of among other I and II has been made by Gleiter and Heilbronner (91). The first three bands in the spectra were assigned to π -orbitals, and good agreement between measured and calculated ionisation potentials was obtained.

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